General

Guideline Title

Diagnosis and treatment of osteoporosis.

Bibliographic Source(s)

Florence R, Allen S, Benedict L, Compo R, Jensen A, Kalogeropoulou D, Kearns A, Larson S, Mallen E, O'Day K, Peltier A, Webb B. Diagnosis and treatment of osteoporosis. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Jul. 87 p. [210 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of osteoporosis. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2011 Jul. 77 p.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC) and the Institute for Clinical Systems Improvement (ICSI): For a description of what has changed since the previous version of this guideline, refer to Summary of Changes Report – July 2013. In addition, ICSI has made a transition to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

The recommendations for the diagnosis and treatment of osteoporosis are presented in the form of a table with a list of evidence-based recommendations and an algorithm with 14 components, accompanied by detailed annotations. An algorithm is provided in the original guideline document at the ICSI Web site for Diagnosis and Treatment of Osteoporosis; clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (Low Quality, Moderate Quality, and High Quality) and strength of recommendation (Weak or Strong) definitions are repeated at the end of the "Major Recommendations" field.

Clinical Highlights

- Discuss risk factors for osteoporosis and primary prevention with all patients presenting for preventive/wellness health visits. (*Annotations #4, 5; Aim #1*)
- Address pharmacologic options for prevention and treatment of osteoporosis with appropriate patients at risk for or who currently have signs and symptoms of osteoporosis. (*Annotation #13; Aims #2, 3*)

Diagnosis and Treatment of Osteoporosis Algorithm Annotations

1. All Patients Presenting for a Preventive/Wellness Visit
   Recommendation:

   - Clinicians should screen for osteoporosis in women aged 65 years of age and older and in younger women whose fracture risk is equal to or greater than 9.3% from Fracture Risk Assessment Tool (FRAX®) analysis or are considered to be at fracture risk *[Strong Recommendation, Moderate Quality Evidence]* (U.S. Preventive Services Task Force, 2011).

   Consider the following:

   - Review risks of osteoporosis with patients during preventive/wellness visits and discuss the importance of maintaining strong bones.
   - Record accurate serial heights and observe for acquired kyphosis.
   - Screening for osteoporosis in men over age 70 and men aged 50 to 69 years of age based on risk factor profile.

   Osteoporosis is the consequence of continued bone loss throughout adulthood, low achieved peak bone mass, or both. The guideline work group recommends maintaining peak bone mass for all patients. To achieve and maintain maximum bone density, patients should have risks for osteoporosis reviewed when they present to their clinician's office. In addition to reviewing historical risk factors (discussed in Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture"), it is important to record accurate serial height measurements with a stadiometer and observe posture for acquired kyphosis. Patients with significant acquired kyphosis and/or an historical height loss greater than 4 cm (1.6 inches) or measured height loss greater than 2 cm (0.8 inches) should have lateral vertebral assessment with dual energy x-ray absorptiometry (DXA) or thoracic and lumbar spine radiographs and bone density testing. Note that the radiation exposure of spinal x-rays are markedly higher than that of vertebral assessment, but the latter is less accessible to clinicians *[Reference]*.

2. Patient with a Low-Impact (Fragility) Fracture
   Consider the following:

   - Consider all adults with a history of vertebral fracture, hip fracture, proximal humerus, ankle, pelvis or distal forearm fracture at higher than average risk for a future fracture.
   - Review lifestyle risk factors for osteoporosis.
     - Discuss adequacy of total calcium and vitamin D intake.
     - Address home safety, fall prevention and specific exercises for muscle strength.
   - Consider bone density testing in patients with fractures who are willing to accept treatment.
   - Consider all men* and postmenopausal women with low-impact (fragility) fracture as potential candidates for pharmacologic intervention, and women and men over age 70 with prior fragility fracture as candidates for osteoporosis therapy even without bone density testing.

   *Although the best data is on postmenopausal women, there may be a similar risk in men, and the guideline work group is including men in this guideline recommendation *[Reference]*.

   Refer to the original guideline document for more information.

3. Patient on or a History of Chronic Glucocorticoid Therapy or Transplant Recipient
   Recommendation:

   - Osteoporosis prevention and treatment measures and bone mineral density (BMD) testing should be considered for anyone who is started on or has been on glucocorticoid therapy (at a dose of more than 5 mg prednisone or equivalent per day for three continuous or more months) *[Strong Recommendation, Moderate Quality Evidence]*.

   Consider the following:

   - Consider all patients for a baseline BMD test at acceptance into a transplantation program, and that follow-up BMD testing be performed yearly prior to transplantation.

   Glucocorticoid Therapy

   Osteoporosis prevention and treatment measures and BMD testing should be considered for anyone who is started on or has been taking or has a history of taking exogenous glucocorticoid therapy (at a dose of more than 5 mg prednisone or equivalent per day for 3 or more months). Osteoporosis prevention measures should also be considered for those who have been or can be expected to be on a daily high-dose inhaled glucocorticoid for several years. While it is never too late in the course of glucocorticoid therapy to prevent or treat osteoporosis, it is preferable to start preventive measures against bone loss when glucocorticoid therapy is started, for two reasons. First, the greatest amount of bone is lost during the first several months of glucocorticoid use. Second, the risk of fracture at any given level of BMD is greater in those on chronic glucocorticoid therapy than in those who are not on a glucocorticoid. That is, fracture risk is

disproportionately increased in those with glucocorticoid-induced low bone density relative to those with low bone density associated with the aging process and/or the postmenopausal state. The loss of bone density on steroids generally totally or nearly totally recovers over a period of months after the steroids have been stopped *[Reference]*.

Refer to the original guideline document for information on BMD loss and fracture associated with oral and inhaled glucocorticoids and mechanisms of bone loss.

Organ Transplantation

Solid organ transplantation of all types and allogeneic bone marrow transplantation are associated with rapid bone loss after transplantation. In addition, many patients develop significant bone loss before transplantation *[Reference]*.

Refer to the original guideline document for more information on pre- and posttransplantation bone loss.

4. Discuss Primary Prevention of Fractures
   Recommendations:

   - Primary prevention should include counseling patients on achievement and maintenance of a normal body mass index (BMI) of 20 to 25 *[Strong Recommendation, Low Quality Evidence]* (Hannan et al., 2000; Hoidrup et al., 1999).
   - A balanced diet including dairy products and appropriate nutrition should be discussed with patients *[Strong Recommendation, Low Quality Evidence]* (Hannan et al., 2000; Hoidrup et al., 1999).
   - Patients should be encouraged and offered assistance in developing a lifetime program of exercise that they will continue to do and enjoy *[Strong Recommendation, Low Quality Evidence]* (Ulrich et al., 1999).
   - Smoking cessation counseling should be done at every visit *[Strong Recommendation, Low Quality Evidence]* (Huopio et al., 2000).
   - Assess risk factors for osteoporosis and osteoporotic fracture *[Strong Recommendation, High Quality Evidence]* (National Osteoporosis Foundation, 2010).

   Consider the following:

   - Women who are prematurely hypogonadal and hypogonadal men should be considered for hormonal replacement therapy to help maintain bone health.

   Body Habitus

   Low BMI (less than 20) is a strong independent risk factor for osteoporosis and fracture. Weight less than 127 pounds, associated with small bones, is a risk factor for osteoporosis *[Reference]*. Primary prevention should include counseling patients on achievement and maintenance of a healthy body weight (BMI between 20 and 25). See also the NGC summary of the ICSI guideline Prevention and management of obesity for adults. A balanced diet including dairy products and appropriate nutrition should be discussed with patients *[Reference]*.

   Gonadal Hormonal Status

   Women who are prematurely hypogonadal and hypogonadal men who are at increased risk for fracture should be considered for hormonal replacement therapy. For further information, please see Annotation #12, "Consider Secondary Causes/Further Diagnostic Testing" as well as Annotation #13, "Address Options for Prevention and Treatment of Osteoporosis/Pharmacologic Intervention if Appropriate/Engage Patient in Shared Decision-Making (SDM)."

   Exercise

   Exercise is well known for its many benefits, both short term and long term. Weight-bearing and muscle-strengthening exercises have been shown to be an integral part of osteoporosis prevention, as well as a part of the treatment process.

   All three components of an exercise program are needed for strong bone health: impact exercise such as jogging, brisk walking, stair climbing; strengthening exercise with weights; and balance training such as Tai Chi or dancing.

   Refer to the original guideline document for more information.

   Cigarette Smoking/Smoking Cessation

   Smoking cessation counseling should be done at every visit. Discussion can include helpful strategies such as nicotine replacement therapy with patches, gum, etc. Bupropion, varenicline, and available smoking cessation classes may also be discussed. For more information on

smoking cessation, please consult the NGC summary of the ICSI guideline Healthy lifestyles.

Alcohol Restriction

Limit alcohol use to *no more than* one drink per day for women and no more than two drinks per day for men. One drink equals 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof distilled spirits. This limit will help to protect bone health and reduce the risk of falls. See Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fractures."

Calcium

Adequate calcium intake from food sources and supplements promotes bone health. When food sources do not provide enough calcium, supplements can be used to meet this goal. Bioavailability of calcium in food sources and supplements is a factor in achieving daily calcium recommendations. See the United States Department of Agriculture (USDA) table for foods rich in calcium (http://www.nal.usda.gov/fnic/foodcomp/search). The goal is to achieve adequate calcium with diet alone if possible.

Calcium Dietary and Supplement Recommendations – General Population Recommendations

- Men and women ages 19-50 years: 1,000 mg/day
- Men ages 51-70: 1,000 mg/day
- Women aged 51 and older: 1,200 mg/day
- Men aged 71 and older: 1,200 mg/day
- Pregnant women and breast feeding aged 18 and older: 1,300 mg/day

Calcium and Vitamin D – Dietary and Supplement Recommendations (National Osteoporosis Foundation, www.nof.org) Recommendations for Those at Risk for Bone Loss

	Calcium	Vitamin D
Adults under age 50	1,000 mg/day	400 IU/day to 800 IU/day
Adults age 50 and older	1,200 mg/day	800 IU/day to 1,000 IU/day

The role of vitamin D in fall prevention remains unclear. The data available for vitamin D supplementation is inconsistent.

Calcium supplementation has been shown to increase the ratio of high-density-lipoprotein (HDL) cholesterol to low-density-lipoprotein (LDL) cholesterol by almost 20% in healthy postmenopausal women by binding to fatty acids in the gut. The effect of calcium supplementation on cardiac risk is unclear at this time. Oversupplementation may be associated with an increased risk of kidney stones and vascular calcification *[Reference]*.

Both low fractional calcium absorption and low dietary calcium intake have been associated with increased fracture risk. Since fractional calcium absorption is affected by multiple factors and decreases with age, adequate lifetime dietary calcium is an important recommendation for bone health *[Reference]*.

Calcium absorption is compromised when oxalic acid is present in foods such as dark, green, leafy vegetables. An exception is soybeans. A variety of foods with calcium is recommended.

Bioavailability from calcium supplements is affected by meals, dose size and tablet disintegration. Calcium absorption efficiency decreases at doses greater than 600 mg; therefore, supplements should be taken with meals and in divided doses. Taking calcium carbonate supplements on an empty stomach may increase the risk of kidney stones and may not be well absorbed. Absorption of calcium carbonate may be decreased in the environment of achlorhydria, high-dose proton-pump inhibitor (PPI) use or histamine receptor blockers when calcium supplement is taken on an empty stomach. Calcium citrate is better absorbed by patients with medication-induced achlorhydria (PPIs, histamine receptor blockers) *[Reference]*.

Calcium slows age-related bone loss.

Calcium may reduce osteoporosis fracture risk.

Vitamin D

Adequate vitamin D intake supports calcium absorption and bone metabolism. Since sunlight exposure cannot be assumed to produce needed vitamin D, dietary and supplement sources are essential. Many adults are deficient in vitamin D, and supplements are often needed to meet daily requirements.

Vitamin D requirements vary with age.

Recommendations of Adequate Intake of Vitamin D from the Institute of Medicine, 2011

- Men/women 18-70: 600 IU/day
- Men/women 71 and older: 800 IU/day

[Reference]

Studies concerning vitamin D and bone health demonstrate daily vitamin D supplementation in the range of 700-800 international units can decrease hip fracture risk in the elderly by 26%, and any non-vertebral fracture by 23% *[Meta-analysis]*.

The effects of optimal vitamin D levels include:

- Maximum suppression of circulating parathyroid hormone (PTH)
- Increased calcium absorption
- Decreased rates of bone loss
- Improved lower extremity functioning *[Meta-analysis] [Reference]*

Refer to the original guideline document for more information on vitamin D.

Prevention of Falls/Increased Likelihood of Falling

Many factors increase the likelihood of falling, and most hip and wrist fractures occur after a fall. Included in these factors are impaired eyesight, certain medications that affect balance, poor health, frailty, low physical function (such as slow gait and speed and decreased quadriceps strength), dementia and history of past falls. Age-related muscle loss (sarcopenia) may also predispose to fall risk *[Reference]*. Preventing falls reduces fractures. Modifying environmental and personal risk factors can be effective in reducing falls. Home visits have been shown to help with this. Also, in some studies, soft or hard hip protector pads have been shown to reduce hip fractures in frail, elderly, adults in community based health care centers. However, adherence in wearing them limits their use and efficacy *[Reference]*.

Please, see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture." Also see the NGC summary of the ICSI guideline Prevention of falls (acute care). Health care protocol.

5. Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture
   The following are risk factors for osteoporosis and osteoporotic fracture:

   - A prior fragility fracture
   - Parental history of hip fracture
   - Current tobacco smoking
   - The use of oral corticosteroids for greater than three continuous months
   - Rheumatoid arthritis
   - Secondary causes of osteoporosis*
   - Daily alcohol use of three or more units daily
   - Advanced age (greater than age 65)
   - Body habitus (weight less than 127 pounds or BMI less than or equal to 20)
   - Caucasian or Asian race
   - Hypogonadism
   - Sedentary lifestyle
   - Diet deficient in calcium or vitamin D without adequate supplementation
   - Increased likelihood of falling

   [Reference]

   *For a list of secondary causes of osteoporosis, please see Appendix A, "Secondary Causes of Osteoporosis," in the original guideline document and Annotation #3, "Patient on or a History of Chronic Glucocorticoid Therapy or Transplant Recipient."

   African-American women have a decreased risk, partly because they begin menopause with a higher BMD and have a lower rates of bone loss after menopause. Besides these, age and prior fracture are also predictors of fracture independent of BMD *[Reference]*.

Refer to the original guideline document for information on relationship of bone mineral loss with body habitus; family history of osteoporosis; cigarette smoking; sedentary lifestyle; alcohol, calcium, and vitamin D intake; and increased likelihood of falling.

6. Low Pretest Probability of Low BMD and Future Fracture Based on Patient Profile
   Bone density testing in general is not recommended for the following individuals who are at low risk of low bone density and future fracture:

   - Premenopausal women who have not had a fracture with minor trauma, are not on chronic glucocorticoid therapy, do not have secondary amenorrhea, and do not have a chronic disease associated with bone loss
   - Eugonadal men less than age 70 who have not had a fracture with minor trauma, are not on glucocorticoid therapy or androgen deprivation therapy, and do not have any significant additional risk factors associated with bone loss
   - Postmenopausal women under age 65 who do not have any significant additional risk factors. See Annotation #8, "High Pretest Probability of Low BMD and Future Fracture Based on Patient Profile/Consider FRAX® Analysis without DXA."

   [Moderate Quality Evidence]

7. Address/Reinforce Options for Prevention of Osteoporosis
   Osteoporosis is the consequence of continued bone loss throughout adulthood, low achieved bone mass, or both. Because of this, clinicians are encouraged to periodically review historical risk factors (see Annotation #4, "Discuss Primary Prevention of Fractures") and primary prevention strategies (see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture") with their patients. Preventive health maintenance exams provide an excellent opportunity for this review.

8. High Pretest Probability of Low BMD and Future Fracture Based on Patient Profile/Consider FRAX® Analysis without DXA
   Consider the following:

   - Risk stratify patients to determine the appropriateness of bone density testing.

   The following individuals are at sufficiently high risk for low bone mass and future fracture that a BMD test is justified to further define that risk. This assumes that the individual being tested is willing to consider pharmacologic treatment for low bone mass documented on a bone density test.

   - Prior fracture with minor trauma (fall from standing height or less)
   - Those who have been or are anticipated to be on glucocorticoid therapy for three or more months at a dose equivalent to or greater than 5 mg prednisone per day
   - Radiographic osteopenia or vertebral deformity consistent with fracture
   - All women 65 years of age or older
   - Postmenopausal women less than age 65:
     - Surgical or natural menopause before age 45
     - Additional risk factors
   - Men over the age of 70 and men aged 50 to 69 years of age based on risk factor profile
   - The FRAX® tool can be used to estimate the 10-year fracture risk based on individual risk factors, in persons who have not had bone density testing. Factors such as low body weight, current smoking, and family history of fragility fracture are included in this calculation.

   [Low Quality Evidence]

   Refer to the original guideline document for more information.

9. Recommend Bone Density Assessment
   Recommendation:

   - Utilize BMD measurement with DXA as it is the single best imaging predictor of fracture risk as well as the best monitor of patient response to treatment *[Strong Recommendation, Moderate Quality Evidence]* (U.S. Preventive Services Task Force, 2011).

   Measurements of BMD with DXA can predict fracture risk and allow for the identification of people who are at increased risk of fracture. Reviews of prospective cohort studies and case control studies have documented a direct relationship between decreasing BMD and increasing bone fracture risk. Additionally, there is evidence that stabilization or increases in BMD with therapy for osteoporosis are associated with substantial reductions in fracture incidence. Therefore, densitometry offers an objective measurement of a patient's response to treatment over time *[Moderate Quality Evidence, Reference]*. At this time there are no cost-effectiveness data for monitoring response to treatment. DXA is ideally performed by a technologist certified by the International Society for Clinical Densitometry (ISCD) or the American Registry of Radiologic Technologists (ARRT).

   Current practice is to describe an individual's BMD as compared to a reference-normal population. In this sense, a T-score is the number of

standard deviations above or below the mean for a gender- and ethnicity-matched young adult healthy population. A T-score is calculated from the following equation:

[(measured BMD - young adult population mean BMD)/young adult population SD]

A Z-score is the number of standard deviations above or below the mean for gender-, ethnicity-, and age-matched healthy population. A Z-score is calculated from the following equation:

[(measured BMD - age-matched population mean BMD)/age-matched population SD]

Normal, low bone density (osteopenia) and osteoporosis are defined by the lowest of lumbar spine (at least two evaluable vertebrae required), femoral neck, and total femur T-score, according to the World Health Organization (WHO). The one-third radius site may be used if either the lumbar spine or femur is non-evaluable. The following classifications apply to postmenopausal women and men age 50 and older:

- Normal: a T-score greater than or equal to -1
- Low bone density (osteopenia): a T-score between -1 and -2.5*
- Osteoporosis: a T-score less than or equal to -2.5
- The term "severe osteoporosis" is reserved for patients with a fragility fracture(s) *and* a T-score less than or equal to -2.5.

*Following a Position Development Conference on bone densitometry in 2005, the International Society of Clinical Densitometry recommends that the term "osteopenia" be retained, but "low bone mass" or "low bone density" are the preferred terms

[Reference]

For patients who decline bone density studies, reinforce osteoporosis prevention.

In premenopausal women, men under age 50, and children, the Z-scores should be used rather than the T-scores in identifying those with low bone density. The WHO classifications should not be used. According to the International Society for Clinical Densitometry: a Z-score of -2.0 or lower is defined as "below the expected range for age" and a Z-score above -2.0 is "within the expected range for age" *[Reference]*.

The Bone Mass Measurement Act of 1998 *[Reference]* broadened the selective screening by mandating Medicare coverage for densitometry services for individuals at risk of osteoporosis as defined by the following criteria:

- An estrogen-deficient woman at clinical risk for osteoporosis
- An individual with vertebral abnormalities
- An individual receiving or planning to receive long-term glucocorticoid therapy greater than or equal to 5.0 mg prednisone/day or an equivalent dose for greater than or equal to 3 months
- An individual with primary hyperparathyroidism
- An individual being monitored to assess the response to or the efficacy of a U.S. Food and Drug Administration (FDA)-approved drug for osteoporosis therapy

The National Osteoporosis Foundation (http://www.NOF.org) also recommends bone density testing in the following:

- Women age 65 and older and men age 70 and older, regardless of clinical risk factors
- Younger postmenopausal women and men age 50 to 69 about whom you have concern based on their clinical risk factor profile
- Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk such as low body weight, prior low-trauma fracture, or high-risk medication
- Adults who have a fragility fracture after age 50
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids in a daily dose greater than or equal to 5 mg prednisone or equivalent for three months or longer) associated with low bone mass or bone loss
- Anyone being considered for pharmacologic therapy for osteoporosis
- Anyone being treated for osteoporosis, to monitor treatment effect
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment
- Postmenopausal women discontinuing estrogen should be considered for bone density testing

[Moderate Quality Evidence]

Refer to Appendix B of the original guideline document for information regarding bone densitometry.

10. Post-Test Probability of Fractures – Use FRAX® Analysis if Osteopenic
Recommendation:

- In cases of osteopenia, the femoral neck T-score should be used in combination with clinical risk factors to predict a given patient's fracture risk in the FRAX® model *[Strong Recommendation, High Quality Evidence]* (Hans, 2011).

Fracture risk in an individual patient is defined as the likelihood of sustaining an osteoporotic fracture over an interval of time. Current fracture risk is defined as the likelihood of an osteoporotic fracture in the patient's remaining lifetime years.

Current fracture risk can be expressed in terms of absolute risk, relative risk, or incidence (annual) risk. Absolute fracture risk is the actual risk of fracture for a given patient. Relative risk of fracture is the ratio of the absolute risk of fracture for the patient compared to the absolute risk of fracture for a young adult-, gender-, and ethnicity-matched reference population. Relative risk of fracture is increased by 1.5 to 3.0 times for each 1.0 standard deviation decrease in bone density below the mean for young adults of the same gender and ethnicity. Fracture risk data in elderly postmenopausal women suggest that fracture prediction is nearly equal regardless of the skeletal site assessed or the type of technology used, with the exception that hip fracture risk is best predicted by proximal femoral BMD measurement *[Reference]*. Similar data are being accumulated for men, although the numbers of studies published so far are much smaller *[Reference]*.

11. Is Risk of Fracture Increased?
Low fracture risk is clinically defined by a BMD T-score above -1.0 (normal bone density by the WHO definition).

Osteoporosis is defined by a BMD T-score of less than or equal to -2.5, and low bone density (osteopenia) is defined as a T-score of -1 to -2.5.

WHO has developed a FRAX® WHO Fracture Risk Assessment Tool that is based on absolute fracture risk. This allows prediction of the 10-year absolute fracture risk for hip fracture and all osteoporotic fractures based on femoral neck bone density. In the absence of femoral neck BMD, total hip BMD may be substituted; however, use of BMD from non-hip sites in the algorithm is not recommended because such use has not been validated. The FRAX® calculation can be found on the Web at http://www.shef.ac.uk/FRAX .

For the U.S. population, treatment continues to be recommended for adults with prior hip or vertebral fragility fracture and adults with osteoporosis by T-score. Treatment is cost effective when the 10-year probability of hip fracture is greater than or equal to 3%, or 10-year probability of any osteoporotic fracture is greater than or equal to 20%. This is a basic tool that should be used in the clinical context of the patient.

Refer to the original guideline document for information regarding FRAX® limitations.

Previous osteoporotic fractures sustained by the patient, history of osteoporotic fractures sustained by the patient's family members, increased rate of bone turnover, the patient's risk of falling, and the use of medications that predispose to falling, also help predict future fracture risk *[Reference]*.

BMD is the single best predictor of future fracture. About 80% of the variance in bone strength and resistance to fracture in animal models is explained by BMD, and numerous studies have demonstrated that fracture risk is predicted by BMD *[Reference]*.

Patients found to have low risk of future fracture by BMD testing should not automatically be assumed to remain at low risk of future fracture over their remaining lifetime years. Patients should be periodically reassessed by reviewing risk factors for osteoporosis, evaluating current primary prevention efforts, reviewing the clinical history for osteoporotic fractures subsequent to the initial bone density evaluation, and measuring BMD. Clinical judgment must be used in determining the appropriate intervals between repeated measurements of BMD over time. Whenever remeasurement occurs, it is ideal to use the same densitometer. In some patients, such as those expected to have high bone turnover and rapid bone loss due to early postmenopausal status, initiation or continuation of steroid therapy, organ transplantation, or other causes, it may be appropriate to remeasure bone density as soon as 6 to 12 months after the initial measurement. In those patients not expected to have high turnover or rapid loss, it is appropriate to remeasure bone density at an appropriate interval, such as 2 to 10 years after the initial assessment depending on baseline bone density, in order to detect patients who lose significant bone density over time. The FRAX® analysis can guide the frequency of the repeat DXAs.

12. Consider Secondary Causes/Further Diagnostic Testing
Recommendation:

- An initial screening laboratory profile should be considered in all patients with osteoporosis *[Strong Recommendation, Low Quality Evidence]*.

Certain diseases are commonly associated with bone loss. These diseases are listed in Appendix A, "Secondary Causes of Osteoporosis,"

in the original guideline document. In broad categories, these include chronic inflammatory autoimmune conditions, endocrinopathies, malignancies, and malabsorptive states.

Recommended initial laboratory evaluation for all patients with osteoporosis without prior workup:

- 25 hydroxy (OH) vitamin D level:
  - Optimal level is greater than or equal to 30 ng/mL in most patients.
  - It is also important to ensure adequate vitamin D stores prior to initiation of advanced pharmacologic osteoporosis therapies.
- Serum calcium:
  - To rule out hypocalcemia (in malabsorption/vitamin D deficiency) or hypercalcemia (in hyperparathyroidism)
  - It is important to correct hypocalcemia prior to initiation of advanced pharmacologic osteoporosis therapies.
- 24-hour urine calcium excretion:
  - This is low in a malabsorptive state (such as in celiac sprue or after gastric bypass), in vitamin D deficiency, or in patients on thiazide diuretics.
  - This is high in idiopathic hypercalciuria (which is a correctable cause of bone loss) in primary hyperparathyroidism and commonly in patients with excessive calcium intake.
- Serum creatinine:
  - This should be drawn in order to screen for renal dysfunction and in order to assure safety of advanced pharmacologic osteoporosis therapies.
- Thyroid-stimulating hormone (TSH):
  - Should be drawn in patients on thyroid hormone supplementation
  - Consider for other patients as clinically indicated.

The following more extensive evaluation for secondary causes of osteoporosis could be considered, on an individual basis, as indicated:

- A biochemical profile that provides information on:
  - Alkaline phosphatase:
    - Elevated in Paget's disease, prolonged immobilization, acute fractures, osteomalacia and other bone diseases
  - Phosphorus:
    - Decreased in osteomalacia
  - Parathyroid hormone level even if serum calcium is normal
- A complete blood count may suggest bone marrow malignancy or infiltrative process (anemia, low white blood cells [WBCs], or low platelets) or malabsorption (anemia, microcytosis, or macrocytosis).
- An elevated sedimentation rate or C-reactive protein may indicate an inflammatory process or monoclonal gammopathy.
- Testosterone (total and free) in men and estradiol (total and bioavailable) in women; luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and prolactin if evidence of hypogonadotropic hypogonadism.
- Tissue transglutaminase if clinical suspicion for gluten enteropathy or low 25-OH vitamin D
- 24-hour urinary free cortisol or overnight dexamethasone suppression test if clinical suspicion of glucocorticoid excess
- Serum and urine protein electrophoresis, with a conditional immunoelectrophoresis

At this time there is no consensus about the routine use of serum and/or urine markers of bone turnover in the evaluation of patients with osteoporosis.

Refer to Appendix A, "Secondary Causes of Osteoporosis," in the original guideline document for a table with the common causes of secondary osteoporosis.

13. Address Options for Prevention and Treatment of Osteoporosis/Pharmacologic Intervention if Appropriate/Engage Patient in Shared Decision-Making (SDM)
    Recommendations:

    - Lifestyle adjustments are universally recommended for bone health *[Strong Recommendation, Moderate Quality Evidence]* (National Osteoporosis Foundation, 2010).
    - Adequate calcium and vitamin D intake as well as regular exercise should be discussed with patients for the prevention of osteoporosis *[Strong Recommendation, Moderate Quality Evidence]* (Heaney, 2000; Ulrich et al., 1999).
    - Bisphosphonates are indicated for reduction of fracture risk (both vertebral and nonvertebral), including postmenopausal women, men and in the setting of glucocorticoid use *[Strong Recommendation, Moderate Quality Evidence]* (Serpa Neto et al., 2012).
    - Once-yearly intravenous zoledronic acid may be given to men and women within 90 days of a hip fracture *[Strong Recommendation, Moderate Quality Evidence]* (Boonen et al., 2011).

- Bisphosphonates, particularly zoledronic acid, should be given to men undergoing androgen deprivation therapy for prostate cancer with osteoporosis and should be considered to prevent bone loss in those without osteoporosis *[Strong Recommendation, Moderate Quality Evidence]* (Serpa Neto et al., 2012).
- Anabolic therapy with parathyroid hormone is indicated for patients with particularly high-risk for future fracture, and data shows reduction in vertebral and non-vertebral fracture *[Strong Recommendation, High Quality Evidence]* (Neer et al., 2001).

Consider the following:

- Nasal calcitonin is now considered a third-line treatment for osteoporosis, but may be useful in some populations for short-term therapy.
- Selective estrogen receptor modulator (SERM) treatment with raloxifene in postmenopausal women has been shown to reduce vertebral fracture risk and is FDA approved for the prevention of breast cancer.
- Receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor, denosumab, has been shown to reduce the cumulative incidence of new vertebral and hip fractures in postmenopausal osteoporosis.
- Means to improve medication adherence, as poor adherence with osteoporosis medications is a large problem. Adherence is associated with significantly fewer fractures.

Please see the medication tables in Appendix C, "Recommended Pharmacologic Agents," of the original guideline document for specific information on pharmacologic agents for treatment and prevention of osteoporosis.

Osteoporosis Prevention (also see Annotation #4, "Discuss Primary Prevention of Fractures") for Patients at High Risk

Estrogen

Estrogen is not currently recommended as a first-line agent in the management or prevention of osteoporosis. It should be used for prevention of postmenopausal osteoporosis only in women at significant risk who cannot take non-estrogen therapies. It is unknown if conclusions of the Women's Health Initiative can be applied to younger (under 50 years of age) postmenopausal women taking estrogen in other doses, formulations or modes of administration.

Calcium and Vitamin D (See Annotation #4, "Discuss Primary Prevention of Fractures")

Bisphosphonates

Bisphosphonates are approved for prevention of postmenopausal women and glucocorticoid-induced osteoporosis. Bisphosphonates and calcitriol therapy may also be effective at preventing bone density loss after transplantation *[Reference]*. Studies indicate that pharmacologic vitamin D preparations or intravenous bisphosphonates (pamidronate, zoledronic, etc.) or oral bisphosphonates (alendronate, risedronate, etc.) are more likely to prevent bone loss after transplantation than calcium and vitamin D with or without calcitonin. BMD testing should be performed every six months to one year until BMD is shown to be stable or improving on therapies for osteoporosis (see Annotation #3, "Patient on or a History of Chronic Glucocorticoid Therapy or Transplant Recipient"). Bisphosphonate therapy should also be considered in men undergoing androgen deprivation therapy for the treatment of prostate cancer to prevent osteoporosis *[Moderate Quality Evidence]*.

Raloxifene

Raloxifene is FDA-approved for the prevention of osteoporosis and prevention of breast cancer in postmenopausal women.

Posttransplantation Bone Loss

Antiresorptive therapy and calcitriol may be effective at preventing bone density loss after transplantation *[Reference]*. Considering the rates of bone loss after transplantation described in Annotation #3, "Patient on Chronic Glucocorticoid Therapy or Transplant Recipient," BMD testing should be performed every six months to one year until BMD is shown to be stable or improving on therapies for osteoporosis. Studies demonstrate that standard calcium and vitamin D supplementation, with or without calcitonin, is not able to prevent bone loss after transplantation. Other studies indicate that pharmacologic vitamin D preparations or intravenous bisphosphonates, such as pamidronate, or zoledronic acid, or oral bisphosphonates, such as alendronate or risedronate, are more likely to prevent bone loss after transplantation.

Osteoporosis Treatment

Bisphosphonates have the strongest data showing risk reductions in both vertebral, hip, and other nonvertebral fractures. Other treatments include raloxifene (see SERM in this annotation) and calcitonin.

Parathyroid hormone 1-34 (teriparatide) (PTH) is used for patients at highest risk for fracture. It could be first-line therapy for those

patients.

In addition to calcium, vitamin D, exercise, physical therapy, surgical repair, and radiologic intervention as appropriate, the therapies listed below may be used. Clinicians should be aware that patient adherence to osteoporosis therapy has been historically poor.

Gonadal Hormone Therapy

Female Gonadal Hormone Therapy

The use of supplemental estrogen in the immediate postmenopause has been well accepted in preventing the rapid loss of bone that occurs in this interval *[Reference]*.

Refer to the original guideline document for more information on female gonadal hormone therapy.

Male Gonadal Hormone Therapy

The bone loss associated with male hypogonadism is reversed by testosterone therapy at least partly via aromatization to estrogen. Testosterone therapy, although not FDA-approved for osteoporosis, seems a reasonable first therapeutic intervention in men symptomatic with hypogonadism who do not have contraindications to the use of testosterone therapy *[Reference]*.

Bisphosphonates

Treatment and Prevention of Osteoporosis in Postmenopausal Women

Alendronate has been shown to increase BMD and reduce the incidence of vertebral, hip, and non-vertebral fractures in postmenopausal women having existing vertebral fractures, and those with low BMD (approximately 2.1 SD below peak) compared to placebo (calcium and vitamin D).

Excellent clinical trial data based on BMD and biomarkers supports the use of oral bisphosphonates for preventing fractures in patients diagnosed with postmenopausal low bone density (osteopenia) or osteoporosis. The best clinical trials have been done with alendronate, risedronate and ibandronate. (See Appendix C, "Recommended Pharmacologic Agents," in the original guideline document.)

Refer to the original guideline document for more information.

Treatment of Osteoporosis in Men

Currently approved therapies for the treatment of osteoporosis in men are alendronate, denosumab, risedronate, zoledronic acid and teriparatide.

Alendronate has been shown to increase BMD at the spine, hip, and total body and to prevent vertebral fractures and height loss in men with osteoporosis *[Reference]*.

Refer to the original guideline document for more information.

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

Clinical trial data supports the use of oral bisphosphonates for reducing bone loss in men and women diagnosed with glucocorticoid-induced bone loss.

Teriparatide is only approved for duration of two years. A gradual decrease in bone mass has been noted after discontinuation of teriparatide therapy; however, immediate follow-up therapy with a bisphosphonate has been shown to preserve the benefits *[Reference]*.

Posttransplantation

Solid organ transplantation of all types and allogeneic bone marrow transplantation are associated with rapid bone loss after transplantation. In addition, many patients develop significant bone loss before transplantation.

Several studies have shown that intravenous pamidronate *[Reference]* and zoledronate *[Reference]* may prevent bone loss after organ transplantation.

Bisphosphonates – Risks Associated with Use

Bisphosphonates and the Risk of Osteonecrosis of the Jaw

There is circumstantial evidence establishing an association between intravenous (IV) bisphosphonates and bisphosphonate-related osteonecrosis of the jaw (BRONJ) in malignancy with the following observations:

- A positive correlation between bisphosphonate potency and risk of BRONJ
- A negative correlation between bisphosphonate potency and duration of bisphosphonate exposure before development of BRONJ
- A positive correlation between the duration of bisphosphonate exposure and developing BRONJ

Causation has not been established. The American Dental Association recommends that all patients on antiresorptive medications for osteoporosis should receive routine dental care. Clinicians should not modify routine dental care solely because of use of oral antiresorptive agents. Discontinuing bisphosphonates just before dental procedures may not lower the risk, but may have negative effects on low bone mass treatment outcomes *[Reference]*.

The American Association of Oral Maxillofacial Surgeons (AAOMS) in the 2009 position paper has developed a working case definition of BRONJ which includes:

- Current or previous treatment with a bisphosphonate
- Exposed bone in the maxillofacial region that has persisted more than eight weeks
- No history of radiation treatment to the jaw

AAOMS has refined the risk factors in their 2009 position paper, including:

- Drug-related risk factors
- Local risk factors
- Demographic and systemic factors
- Genetic factors (in multiple myeloma)
- Preventive factors

Treatment goals, staging and strategies for BRONJ are also noted in this source.

Bisphosphonates and Risk of Atrial Fibrillation

Studies have suggested that at least some postmenopausal women taking oral or intravenous bisphosphonates for osteoporosis may be at increased risk of atrial fibrillation. The HORIZON Trial *[Reference]* demonstrated an unexpected mildly increased risk of serious atrial fibrillation. This was not seen in a subsequent trial of postmenopausal women following hip fracture that showed that zoledronic acid reduced fractures and mortality but did not show an increased incidence of atrial fibrillation in this older population at higher risk of atrial fibrillation *[Reference]*. Reanalysis of the Fracture Intervention Trial with alendronate and a retrospective review of risedronate data did not show an increased risk of atrial fibrillation *[Reference]*. Conflicting data is reported from two separate population-based case control studies *[Reference]*. In light of the conflicting results from these studies, it is premature to stop oral or intravenous bisphosphonates in patients with postmenopausal osteoporosis due to concerns about atrial fibrillation. Patients who are currently on bisphosphonates are advised to continue their medication as prescribed and to direct any questions they have about their medication to their health care clinician.

Bisphosphonates and Risk of Subtrochanteric Fracture

There is concern that bisphosphonate use is associated with an increased risk of atypical femoral fracture. A large observational study showed increased rates of atypical femoral fractures in people taking alendronate; however, larger cumulative doses were not associated with higher rates of atypical femoral fractures compared to smaller cumulative doses, suggesting fractures maybe associated with osteoporosis rather than bisphosphonate use *[Reference]*.

Refer to the original guideline document for additional information regarding risks associated with bisphosphonate use.

Selective Estrogen Receptor Modulator (SERM)

The only SERM approved for the prevention and treatment of osteoporosis is raloxifene.

The MORE trial was a large 3-year randomized placebo-controlled study in postmenopausal women with osteoporosis. Raloxifene showed an increase in BMD and reduced the risk of vertebral fractures. The risk of non-vertebral fractures did not differ between placebo and raloxifene. There was an increased risk of venous thromboembolism compared with placebo (relative risk [RR] 3.1, 95% confidence interval [CI] 1.5-6.2) *[Reference]*.

The CORE 4-year trial extension of 4,011 women continuing from MORE (7,705) showed no difference in overall mortality, cardiovascular events, cancer or nonvertebral fracture rates *[Reference]*.

In the STAR trial *[Reference]*, raloxifene was found comparable to tamoxifen for the prevention of invasive breast cancer. Thus, raloxifene appears to be the drug of choice for women with osteoporosis if the main risk is of spinal fracture and there is an elevated risk of breast cancer.

Calcitonin

Treatment of Osteoporosis in Postmenopausal Women

Nasal salmon-calcitonin 200 international units daily has shown a 33% risk reduction in new vertebral fractures compared with placebo (RR 0.67, 95% CI 0.47-0.97, p = 0.03). This occurred without significant effects on BMD. BMD measurements were not blinded to investigators and 59% (744) of participants withdrew from the study early. Also, a dose response was not observed with respect to risk reduction of vertebral fractures *[Reference]*. Other more efficacious agents have largely replaced the use of this agent except in rare clinical cases.

Posttransplantation

Several studies have shown that nasal spray calcitonin has little effect on prevention of bone loss after organ or bone marrow transplantation *[Reference]*.

Refer to the original guideline document for information on anabolic agents; denosumab; strontium ranelate; combination therapy (estrogen and bisphosphonates); comparative trials; calcitriol-1 25-OH vitamin D; alternative and complementary agents (phytoestrogens, ipriflavone, natural progesterone, magnesium, vitamin K, eicosapentaenoic and gamma-linolenic acid supplementation, and kampo formulae).

Adherence to Medications for Bone Loss

Adherence (compliance + persistence) is a major problem with medications for bone loss. The literature suggests that 45% to 50% of patients on one of these agents have stopped them within one year *[Reference]*. Adherence to therapy was associated with significantly fewer fractures at 24 months *[Reference]*. The use of follow-up bone densitometry and bone markers has not been shown to improve adherence. Follow-up phone calls or visits have shown improvement in adherence *[Reference]*. Although not studied, a close relationship with a primary care clinician who thoroughly discusses the rationale, risks and benefits of treatment most likely improves adherence significantly, especially if followed up by a phone call or visit. Several studies support weekly bisphosphonate dosing versus daily, and/or monthly dosing versus weekly to improve compliance *[Reference]*. It is important to include the patient in discussions related to their treatment options. Shared Decision-Making (SDM) is a model that facilitates these discussions. Please see Appendix D in the original guideline document for more information on this model.

Treatment Failure

There is no consensus as to what constitutes a true treatment failure for patients on pharmacologic treatment for bone loss. It is unclear if an intercurrent fracture once on a medication for at least a year is a treatment failure, but generally it is considered as such, assuming there is no other cause for lack of efficacy. A significant decrease in bone density on treatment is generally considered a treatment failure, but is quite unusual. Other more common causes of such a decrease must first be ruled out; patient not taking the medication or not taking it as scheduled or properly (bisphosphonate), malabsorption, calcium or vitamin D deficiency or an unrecognized secondary cause of bone loss. In case of treatment failure, an alternative agent or combination therapy should be considered.

14. Follow-Up Testing (Lab Work and DXA if Indicated)
    Sequential bone density testing using central DXA may be useful, and is generally suggested in monitoring drug therapy for the treatment of osteopenia or osteoporosis *[Reference]*. The utility follow-up bone densitometry depends on the quality control of the DXA center. There is a lack of evidence supporting the value of frequent repeat densitometry. It remains a controversial topic. At this point the work group suggests that such testing be considered no more than every 12 to 24 months. A frequency as often as every 6 to 12 months may be indicated in the case of glucocorticoid treated patients or those on suppressive doses of thyroid hormone. Other patients at risk for accelerated bone loss include women at early menopause or those who have discontinued estrogen and are not on another bone protective agent.* The lumbar spine and the total proximal femur have the highest reproducibility and are the preferred sites for monitoring therapy *[Reference]*. Changes in BMD should only be reported as significant if they exceed the "least significant change" for the DXA center *[Reference]*. Stability or increase in BMD indicates successful therapy. A significant decline in BMD may require further investigation.

    A significant decrease in BMD on therapy may be due to:

    - Poor drug adherence
    - Improper medication administration technique in the case of bisphosphonates

- A missed secondary cause of osteoporosis (e.g., hyperparathyroidism, malabsorption)
- Inadequate calcium intake
- Untreated Vitamin D deficiency
- A true treatment failure due to the drug itself
- Malabsorption of orally administered drugs

Further follow-up BMD testing after stability or improvement over three to four years has been demonstrated is recommended by most experts. No study has been done as to whether follow-up BMD testing on therapy enhances fracture risk reduction but it may affect patient adherence to therapy *[Reference]*. Therapy should not be withheld if follow-up bone density testing is not available.

*Medicare provides coverage for bone densitometry with central DXA every two years to monitor osteoporosis therapy.

Definitions:

Quality of Evidence and Strength of Recommendations

Category	Quality Definitions	Strong Recommendation	Weak Recommendation
High Quality Evidence	Further research is very unlikely to change confidence in the estimate of effect.	The work group is confident that the desirable effects of adhering to this recommendation outweigh the undesirable effects. This is a strong recommendation for or against. This applies to most patients.	The work group recognizes that the evidence, though of high quality, shows a balance between estimates of harms and benefits. The best action will depend on local circumstances, patient values or preferences.
Moderate Quality Evidence	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.	The work group is confident that the benefits outweigh the risks, but recognizes that the evidence has limitations. Further evidence may impact this recommendation. This is a recommendation that likely applies to most patients.	The work group recognizes that there is a balance between harms and benefit, based on moderate quality evidence, or that there is uncertainty about the estimates of the harms and benefits of the proposed intervention that may be affected by new evidence. Alternative approaches will likely be better for some patients under some circumstances.
Low Quality Evidence	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change. The estimate or any estimate of effect is very uncertain.	The work group feels that the evidence consistently indicates the benefit of this action outweighs the harms. This recommendation might change when higher quality evidence becomes available.	The work group recognizes that there is significant uncertainty about the best estimates of benefits and harms.

Clinical Algorithm(s)

A detailed and annotated clinical algorithm titled "Diagnosis and Treatment of Osteoporosis" is provided in the original guideline document .

Scope

Disease/Condition(s)

Osteoporosis and osteoporotic fractures

Guideline Category

Counseling

Diagnosis

Evaluation

Prevention

Risk Assessment

Screening

Treatment

Clinical Specialty

Endocrinology

Family Practice

Geriatrics

Internal Medicine

Obstetrics and Gynecology

Preventive Medicine

Rheumatology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Health Plans

Hospitals

Managed Care Organizations

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To increase the percentage of female patients age 18 years and older who are evaluated for osteoporosis risk factors during a preventive visit
- To increase the percentage of female and male patients age 50 years and older and diagnosed with osteoporosis who receive treatment for osteoporosis
- To improve diagnostic and therapeutic follow-up for osteoporosis of adults presenting with a history of low-impact (fragility) fracture for men and women age 50 or older

Target Population

Adult patients at risk for osteoporosis or with suspected or confirmed osteoporosis

Note: This guideline does not address the pediatric population in which a low bone mass leading to fracture is very rare and pharmacologic intervention is only occasionally indicated.

Interventions and Practices Considered

Diagnosis/Risk Assessment/Evaluation/Screening

1. Assessment for and discussion of risk factors for osteoporosis and low-impact fracture
2. Use of fracture risk assessment tool (FRAX® analysis)
3. Serial height measurements with a stadiometer
4. Assessment of posture for kyphosis
5. Lateral vertebral assessment with dual energy x-ray absorptiometry (DXA) or radiographs of the thoracic and lumbar spine as indicated
6. Measurement of bone mineral density (BMD) as indicated, including bone densitometry screening of women age 65 and older and men age 70 and older
7. Vertebral fracture assessment (VFA)
8. Laboratory evaluation of patients with osteoporosis to assess for secondary causes of osteoporosis (tests vary depending on patient features)

Prevention/Treatment

1. Shared decision-making
2. Lifestyle counseling regarding measures to prevent fractures (exercise, smoking cessation, alcohol restriction, dietary counseling, weight, environmental modification to prevent falls, measures to reduce the impact of falls [such as soft hip protector pads])
3. Vitamin D and calcium supplementation
4. Pharmacologic agents
    - Gonadal hormones (estrogen preventive therapy in women and testosterone for hypogonadism in men)
    - Bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid)
    - Selective estrogen receptor modulator (SERM) (raloxifene)
    - Calcitonin (calcitonin-salmon nasal spray)
    - Parathyroid hormone 1-34 (teriparatide)
    - Denosumab
5. Follow-up BMD testing (with DXA) at a central site after pharmacologic intervention to assess changes in BMD

Notes:

> Routine supplementation with the following alternative and complementary agents has either not been studied or not shown benefit for treatment of osteoporosis: phytoestrogens, ipriflavone, natural progesterone, magnesium, vitamin K, eicosapentaenoic acid and gamma-linolenic acid supplementation, and kampo formulae
> The guideline developers listed and commented on the following non-U.S. Food and Drug Administration (FDA)-approved treatments for osteoporosis: bisphosphonates: etidronate, pamidronate; calcitriol; cholecalciferol; ergocalciferol; nandrolone decanoate; sodium fluoride; tamoxifen; tibolone; and strontium ranelate

Major Outcomes Considered

- Fracture risk (absolute risk, relative risk, and incidence)
- Predictive value of bone mineral density measurements
- Effects of prevention/treatment interventions on bone density, bone loss, bone health, and fracture risk
- Adverse effects of medications

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A consistent and defined process is used for literature search and review for the development and revision of Institute for Clinical Systems Improvement (ICSI) guidelines. The literature search was divided into two stages to identify systematic reviews (stage I) and randomized controlled trials (stage II). Literature search terms used for this revision include frequency of DXA, primary and secondary workups, fracture risk assessment (FRAX®), calcium as it pertains to cardiovascular risk, osteoporosis in men, vitamin D and Prolia (denosumab) in PubMed from January 2010 through January 2013.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence and Strength of Recommendations

Category	Quality Definitions	Strong Recommendation	Weak Recommendation
High Quality Evidence	Further research is very unlikely to change confidence in the estimate of effect.	The work group is confident that the desirable effects of adhering to this recommendation outweigh the undesirable effects. This is a strong recommendation for or against. This applies to most patients.	The work group recognizes that the evidence, though of high quality, shows a balance between estimates of harms and benefits. The best action will depend on local circumstances, patient values or preferences.
Moderate Quality Evidence	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.	The work group is confident that the benefits outweigh the risks, but recognizes that the evidence has limitations. Further evidence may impact this recommendation. This is a recommendation that likely applies to most patients.	The work group recognizes that there is a balance between harms and benefit, based on moderate quality evidence, or that there is uncertainty about the estimates of the harms and benefits of the proposed intervention that may be affected by new evidence. Alternative approaches will likely be better for some patients under some circumstances.
Low Quality Evidence	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change. The estimate or any estimate of effect is very uncertain.	The work group feels that the evidence consistently indicates the benefit of this action outweighs the harms. This recommendation might change when higher quality evidence becomes available.	The work group recognizes that there is significant uncertainty about the best estimates of benefits and harms.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline Development Process

A work group consisting of 6 to 12 members that includes physicians, nurses, pharmacists, other healthcare professionals relevant to the topic, and an Institute for Clinical Systems Improvement (ICSI) staff facilitator develops each document. Ordinarily, one of the physicians will be the leader. Most work group members are recruited from ICSI member organizations, but if there is expertise not represented by ICSI members, 1 or 2 work group members may be recruited from medical groups, hospitals or other organizations that are not members of ICSI. Patients on occasion are invited to serve on work groups.

The work group will meet for 7 to 8 three-hour meetings to develop the guideline. A literature search and review is performed and the work group members, under the coordination of the ICSI staff facilitator, develop the algorithm and write the annotations and literature citations.

Once the final draft copy of the guideline is developed, the guideline goes to the ICSI members for critical review.

Revision Process of Existing Guidelines

ICSI scientific documents are revised every 12 to 24 months as indicated by changes in clinical practice and literature. For documents that are revised on a 24-month schedule, ICSI checks with the work group on an annual basis to determine if there have been changes in the literature significant enough to cause the document to be revised earlier or later than scheduled. For yearly reviewed documents, ICSI checks with every work group 6 months before the scheduled revision to determine if there have been changes in the literature significant enough to cause the document to be revised earlier than scheduled.

Literature Search

ICSI staff, working with the work group to identify any new pertinent clinical trials, systematic reviews, or regulatory statements and other professional guidelines, conduct a literature search.

Revision

The work group will meet for 1 to 2 three-hour meetings to review the literature, respond to member organization comments, and revise the document as appropriate.

A second review by members is indicated if there are changes or additions to the document that would be unfamiliar or unacceptable to member organizations. If a review by members is not needed, the document goes to the appropriate steering committee for approval according to the criteria outlined in the "Description of Method of Guideline Validation" field.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

- The National Osteoporosis Foundation (NOF) conducted a cost-effectiveness analysis regarding the prevention, detection and treatment of osteoporosis. They concluded that bone densitometry was reasonable for all women over age 65, and for postmenopausal women under

age 65 with one of the following risk factors: thin body habitus, family history of fracture and current cigarette smoking.
- The World Health Organization (WHO) has developed a FRAX® WHO Fracture Risk Assessment Tool that is based on absolute fracture risk. This allows prediction of the 10-year absolute fracture risk for hip fracture and all osteoporotic fractures based on femoral neck bone density. For the U.S. population, treatment continues to be recommended for adults with prior hip or vertebral fragility fracture and adults with osteoporosis by T-score. Treatment is cost effective when the 10-year probability of hip fracture is greater than or equal to 3%, or 10-year probability of any osteoporotic fracture is greater than or equal to 20%. This is a basic tool that should be used in the clinical context of the patient.
- Two studies were done to evaluate for a cost-effective testing strategy for secondary causes of osteoporosis. They found that 25-hydroxy vitamin D level, serum calcium, 24-hour urine calcium excretion, serum creatinine, and thyroid-stimulating hormone, along with a parathyroid hormone (PTH), were enough to diagnose most secondary causes in women who appeared healthy. The guideline developers counter that a PTH may not initially be needed because the serum calcium and vitamin D levels, if abnormal, would catch most cases of secondary hyperparathyroidism.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Critical Review Process

The purpose of critical review is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the guideline. Critical review also provides an opportunity for clinicians in each group to come to consensus on feedback they wish to give the work group and to consider changes necessary across systems in their organization to implement the guideline.

All member organizations are expected to respond to critical review guidelines. Critical review of guidelines is a criterion for continued membership within Institute for Clinical Systems Improvement (ICSI).

After the critical review period, the guideline work group reconvenes to review the comments and make changes, as appropriate. The work group prepares a written response to all comments.

Document Approval

Each document is approved by the Committee for Evidence-Based Practice (CEBP).

The committee will review and approve each guideline/protocol, based on the following criteria:

- The aim(s) of the document is clearly and specifically described.
- The need for and importance of the document is clearly stated.
- The work group included individuals from all relevant professional groups and had the needed expertise.
- Patient views and preferences were sought and included.
- The work group has responded to all feedback and criticisms reasonably.
- Potential conflicts of interest were disclosed and do not detract from the quality of the document.
- Systematic methods were used to search for the evidence to assure completeness and currency.
- Health benefits, side effects, risks and patient preferences have been considered in formulating recommendations.
- The link between the recommendation and supporting evidence is clear.
- Where the evidence has not been well established, recommendations based on community practice or expert opinion are clearly identified.
- Recommendations are specific and unambiguous.
- Different options for clinical management are clearly presented.
- Clinical highlights and recommendations are easily identifiable.
- Implementation recommendations identify key strategies for *health care systems* to support implementation of the document.
- The document is supported with practical and useful tools to ease *clinician* implementation.
- Where local resource availability may vary, alternative recommendations are clear.
- Suggested measures are clear and useful for quality/process improvement efforts.

Once the document has been approved, it is posted on the ICSI Web site and released to members for use.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Boonen S, Orwoll E, Magaziner J, ColonEmeric CS, Adachi JD, BucciRechtweg C, Haentjens P, Kaufman JM, Rizzoli R, Vanderschueren D, Claessens F, Sermon A, Witvrouw R, Milisen K, Su G, Lyles KW. Once-yearly zoledronic acid in older men compared with women with recent hip fracture. J Am Geriatr Soc. 2011 Nov;59(11):2084-90. PubMed

Hannan MT, Felson DT, DawsonHughes B, Tucker KL, Cupples LA, Wilson PW, Kiel DP. Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. J Bone Miner Res. 2000 Apr;15(4):710-20. PubMed

Hans DB, Kanis JA, Baim S, Bilezikian JP, Binkley N, Cauley JA, Compston JE, Cooper C, DawsonHughes B, ElHajj Fuleihan G, Leslie WD, Lewiecki EM, Luckey MM, McCloskey EV, Papapoulos SE, Poiana C, Rizzoli R. Joint Official Positions of the International Society for Clinical Densitometry and International Osteoporosis Foundation on FRAX((R)). Executive Summary of the 2010 Position Development Conference on Interpretation and use of FRAX(R) in clinical practice. J Clin Densitom. 2011 Jul-Sep;14(3):171-80. PubMed

Heaney RP. Calcium, dairy products and osteoporosis. J Am Coll Nutr. 2000 Apr;19(2 Suppl):83S-99S. PubMed

Hoidrup S, Gronbaek M, Pedersen AT, Lauritzen JB, Gottschau A, Schroll M. Hormone replacement therapy and hip fracture risk: effect modification by tobacco smoking, alcohol intake, physical activity, and body mass index. Am J Epidemiol. 1999 Nov 15;150(10):1085-93. PubMed

Huopio J, Kroger H, Honkanen R, Saarikoski S, Alhava E. Risk factors for perimenopausal fractures: a prospective study. Osteoporos Int. 2000;11(3):219-27. PubMed

National Osteoporosis Foundation (NOF). Clinician's guide to prevention and treatment of osteoporosis. Washington (DC): National Osteoporosis Foundation (NOF); 2010. 44 p.

Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001 May 10;344(19):1434-41. PubMed

Serpa Neto A, TobiasMachado M, Esteves MA, Senra MD, Wroclawski ML, Fonseca FL, Dos Reis RB, Pompeo AC, Giglio AD. Bisphosphonate therapy in patients under androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2012 Mar;15(1):36-44. PubMed

U.S. Preventive Services Task Force. Screening for osteoporosis: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2011 Mar 1;154(5):356-64. PubMed

Ulrich CM, Georgiou CC, Gillis DE, Snow CM. Lifetime physical activity is associated with bone mineral density in premenopausal women. J Womens Health. 1999 Apr;8(3):365-75. PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate recognition, prevention, and treatment of osteoporosis and subsequent decrease in bone loss and fracture risk and increase in bone health

Potential Harms

- Oversupplementation of calcium may be associated with an increased risk of kidney stones and vascular calcification. Taking calcium carbonate supplements on an empty stomach may increase the risk of kidney stones and may not be well absorbed.
- Hot flashes, leg cramps, and increased risk of venous thromboembolic events are reported side effects of raloxifene.
- Oral bisphosphonate preparations have the potential to cause esophagitis, abdominal pain, esophageal ulcer, diarrhea, musculoskeletal pain, acid regurgitation, dyspepsia, dysphagia, flu-like symptoms (rare), atrial fibrillation, jaw osteonecrosis (on rare occasions), and transient increase in creatinine.
- Side effects of calcitonin include nausea, flushing, and rhinitis with nasal spray.
- Adverse effects of estrogen are bloating; breast tenderness; uterine bleeding; increased risk of myocardial infarction, stroke, venous thrombosis or pulmonary embolism, and breast cancer. Dementia, gall bladder disease, hypercalcemia, visual abnormalities, and hypertension are also mentioned.
- Side effects of denosumab include pain (back, extremity and musculoskeletal); hypercholesterolemia; cystitis; infectious disease; rash; hypocalcemia; aseptic necrosis of the jaw (rare); and atypical femoral fracture.
- Parathyroid hormone (teriparatide) is shown to cause an increase in the incidence of osteosarcoma in male and female rats, dependent on dose and duration of treatment; orthostatic hypotension; increase in serum calcium; increase in urinary calcium; and increase in serum uric acid.

See Appendix C in the original guideline document for a more complete list of adverse drug reactions.

Contraindications

Contraindications

- Contraindications to alendronate include abnormalities of the esophagus that delay esophageal emptying, inability to stand or sit upright for at least 30 minutes, hypersensitivity, and uncorrected hypocalcemia. It is not recommended for patients with creatinine clearance (CrCl) ≤35 mL/min.
- Contraindications to ibandronate include uncorrected hypocalcemia, inability to stand or sit upright for at least 60 minutes, and hypersensitivity. It is not recommended for patients with CrCl ≤30 mL/min.
- Contraindications to risedronate and risedronate delayed release include inability to stand or sit upright for at least 30 minutes, hypersensitivity, and uncorrected hypocalcemia. It is not recommended for patients with CrCl ≤30 mL/min.
- Contraindications to zoledronic acid include hypersensitivity to zoledronic acid or any of its excipients and uncorrected hypocalcemia. It is not recommended for patients with CrCl ≤35 mL/min.
- Contraindications to raloxifene include pregnancy, history of venous thromboembolism, hypersensitivity, and nursing.
- Contraindications to teriparatide include Paget's disease, prior therapeutic radiation therapy involving the skeleton, bone metastases or history of skeletal malignancies, metabolic bone disease (other than osteoporosis), hypercalcemia, pregnant and nursing women, unexplained elevated alkaline phosphatase, hypersensitivity, and pediatric population or young adults with open epiphyses.
- Contraindications to calcitonin-salmon include hypersensitivity.
- Contraindications to estrogens include pregnancy; history of thromboembolic disorders; breast cancer (except appropriately selected patients treated for metastatic disease); estrogen dependent neoplasia; undiagnosed abnormal vaginal bleeding; hypersensitivity; liver

dysfunction or disease, active or recent (within one year); and stroke or myocardial infarction.
- Contraindications to denosumab include uncorrected pre-existing hypocalcemia

Qualifying Statements

Qualifying Statements

- The information contained in this Institute for Clinical Systems Improvement (ICSI) Health Care Guideline is intended primarily for health professionals and other expert audiences.
- This ICSI Health Care Guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients and families are urged to consult a health care professional regarding their own situation and any specific medical questions they may have. In addition, they should seek assistance from a health care professional in interpreting this ICSI Health Care Guideline and applying it in their individual case.
- This ICSI Health Care Guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition.
- There are very limited data from randomized controlled trials of alternative and complementary agents for prevention or treatment of osteoporosis.

Implementation of the Guideline

Description of Implementation Strategy

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

Detailed measurement strategies are presented to help close the gap between clinical practice and the guideline recommendations. Summaries of the measures are provided in the National Quality Measures Clearinghouse (NQMC).

Implementation Tools

Clinical Algorithm

Quality Measures

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Related NQMC Measures

Diagnosis and treatment of osteoporosis: percentage of patients who were assessed for risk factors for osteoporosis during an annual preventive visit.

Diagnosis and treatment of osteoporosis: percentage of patients who were found to be at risk for bone loss or fractures who had bone densitometry.

Diagnosis and treatment of osteoporosis: percentage of patients with whom adequacy of vitamin D and calcium dietary supplementation were addressed.

Diagnosis and treatment of osteoporosis: percentage of patients diagnosed with osteoporosis who are on pharmacologic therapy.

Diagnosis and treatment of osteoporosis: percentage of patients with a history of low-impact (fragility) fracture who were assessed for osteoporosis.

Diagnosis and treatment of osteoporosis: percentage of patients with a history of low-impact (fragility) fracture assessed for secondary causes of osteoporosis.

Diagnosis and treatment of osteoporosis: percentage of patients with a history of low-impact (fragility) fracture and diagnosed with osteoporosis due to secondary causes offered treatment.

Diagnosis and treatment of osteoporosis: percentage of patients with a low-impact (fragility) fracture who are taking calcium and vitamin D dietary supplementation.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Florence R, Allen S, Benedict L, Compo R, Jensen A, Kalogeropoulou D, Kearns A, Larson S, Mallen E, O'Day K, Peltier A, Webb B. Diagnosis and treatment of osteoporosis. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2013 Jul. 87 p. [210 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2002 Aug (revised 2013 Jul)

Guideline Developer(s)

Institute for Clinical Systems Improvement - Nonprofit Organization

Guideline Developer Comment

The Institute for Clinical Systems Improvement (ICSI) is comprised of 50+ medical group and hospital members representing 9,000 physicians in Minnesota and surrounding areas, and is sponsored by five nonprofit health plans. For a list of sponsors and participating organizations, see the ICSI Web site.

Source(s) of Funding

- The Institute for Clinical Systems Improvement (ICSI) provided the funding for this guideline. The annual dues of the member medical groups and sponsoring health plans fund ICSI's work. Individuals on the work group are not paid by ICSI, but are supported by their medical group for this work.
- ICSI facilitates and coordinates the guideline development and revision process. ICSI, member medical groups, and sponsoring health plans review and provide feedback, but do not have editorial control over the work group. All recommendations are based on the work group's independent evaluation of the evidence.

Guideline Committee

Committee on Women's Health

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

The Institute for Clinical Systems Improvement (ICSI) has long had a policy of transparency in declaring potential conflicting and competing interests of all individuals who participate in the development, revision and approval of ICSI guidelines and protocols.

In 2010, the ICSI Conflict of Interest Review Committee was established by the Board of Directors to review all disclosures and make recommendations to the board when steps should be taken to mitigate potential conflicts of interest, including recommendations regarding removal of work group members. This committee has adopted the Institute of Medicine Conflict of Interest standards as outlined in the report Clinical Practice Guidelines We Can Trust (2011).

Where there are work group members with identified potential conflicts, these are disclosed and discussed at the initial work group meeting. These members are expected to recuse themselves from related discussions or authorship of related recommendations, as directed by the Conflict of Interest committee or requested by the work group.

The complete ICSI policy regarding Conflicts of Interest is available at the ICSI Web site.

Disclosure of Potential Conflicts of Interest

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Financial/Non-financial Conflicts of Interest: None

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Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of osteoporosis. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2011 Jul. 77 p.

Guideline Availability

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site .

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org ; e-mail: icsi.info@icsi.org.

Availability of Companion Documents

The following is available:

- Diagnosis and treatment of osteoporosis. Executive summary. Bloomington (MN): Institute for Clinical Systems Improvement, 2013 Jul. Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site .

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org ; e-mail: icsi.info@icsi.org.

Patient Resources

None available

NGC Status

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Testosterone Products. This summary was updated by ECRI Institute on April 8, 2015 following the U.S. Food and Drug Administration advisory on Chantix (varenicline).

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